

RESEARCH ARTICLE

View Article Online
View Journal | View IssueCite this: *Org. Chem. Front.*, 2021, 8, 6074

N-Heterocyclic carbene-catalyzed radical ring-opening acylation of oxime esters with aldehydes†

Zhihao Zhang,^a Xin Zou,^a Zhenjiang Li,^b *^{a,b} Yu Gao,^a Yuanyuan Qu,^a Yusheng Quan,^a Yi Zhou,^a Jinlan Li,^a Jie Sun,^c and Kai Guo,^b *^{a,b}Received 9th July 2021,
Accepted 30th August 2021
DOI: 10.1039/d1qo01015h
rsc.li/frontiers-organicA cross-coupling of cycloketone oxime esters with aldehydes catalyzed by N-heterocyclic carbenes *via* a radical pathway was established. This modular protocol features easy operation, no external oxidants or reductants, and a broad functional group compatibility. The merit of this method was showcased by late-stage modification of complicated aldehydes derived from the medical intermediate pregnenolone and natural product diacetone-D-glucose.

Introduction

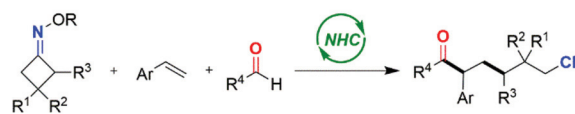
Owing to their unique nucleophilicity and Lewis basicity, N-heterocyclic carbenes (NHCs) have arisen as prominent organocatalysts with wide applications in chemical synthesis.¹ Commonly, NHC-catalyzed transformations proceed by the generation of Breslow,² π -extended Breslow³ or acyl azolium intermediates⁴ in electron-pair-transfer pathways. In contrast, the emerging realm of NHC catalyzed single-electron-transfer (SET) reactions still remains underdeveloped,⁵ but has opened new avenues for developing novel catalytic modes and promising synthetic strategies.⁶ Thus, the development of novel reaction types *via* radical NHC catalysis is highly desirable.

Since the pioneering disclosure of the reducing ability of the enolate form of the Breslow intermediate by the Fukuzumi group,⁷ elegant radical transformations mediated by NHCs have been reported by Scheidt,⁸ Studer,⁹ Rovis,¹⁰ Chi,¹¹ Ye,¹² Ohmiya,¹³ and other groups.¹⁴ Recently, we also developed a regioselective, intermolecular 1,2-cyanoalkylacylation of alkenes with oxime esters¹⁵ and aldehydes by NHC organocatalysis (Scheme 1A).¹⁶ A SET from the enolate form of the Breslow intermediate to a cyclobutanone oxime ester occurs to give a persistent aldehyde-derived ketyl radical and a transient

primary cyanoalkyl radical after radical transposition *via* C–C bond cleavage. Radical addition of the primary cyanoalkyl radical to styrene occurs preferentially to lead to the more stable benzyl radical, which then engages in radical–radical cross-coupling with the persistent ketyl radical to afford the three-component coupling product.

Enlightened by this finding, we surmised that if the cycloketone oxime esters themselves can form the more stable benzyl radicals, the direct radical cross-coupling of aldehydes with such cycloketone oxime esters might be realized. Herein, we report an NHC-catalyzed radical ring-opening acylation of oxime esters with aldehydes under transition-metal-free and redox-neutral conditions, granting a straightforward, flexible access to ketonitrile structures (Scheme 1B). It is noteworthy that the products are a class of versatile building blocks.

A. NHC-catalyzed 1,2-cyanoalkylacylation of alkenes (our previous work)



B. NHC-catalyzed ring-opening acylation of oxime esters (this work)



Scheme 1 Synthetic strategy.

^aCollege of Biotechnology and Pharmaceutical Engineering, Nanjing Tech University, 30 Puzhu Road South, Nanjing 211816, P. R. China. E-mail: zjli@njtech.edu.cn^bState Key Laboratory of Materials-Oriented Chemical Engineering, Nanjing Tech University, 30 Puzhu Road South, Nanjing 211816, P. R. China. E-mail: guok@njtech.edu.cn^cCollege of Food Science and Light Industry, Nanjing Tech University, 30 Puzhu Road South, Nanjing 211816, P. R. China

†Electronic supplementary information (ESI) available. See DOI: 10.1039/d1qo01015h

Results and discussion

At the outset, 4-methylbenzaldehyde **1a** and *O*-(*tert*-butoxycarbonyl) oxime **2a** were chosen as model substrates to investigate the ring-opening acylation of oxime esters in the presence of the carbene precursor. Indeed, in our most recent work,¹⁶ the two-component cross-coupling of an oxime and an aldehyde was observed;¹⁷ thus a brief optimization of the carbene catalyst, solvent, and base led to the identification of optimal conditions, which involved the use of the *N*-2,6-diisopropylphenyl-substituted cycloheptane-fused thiazolium precatalyst **C1** (20 mol%), dichloromethane (DCM), and cesium carbonate to furnish the two-component coupling product ketonitrile **3aa** in 95% yield (Table 1, entry 1).

It was found that both the backbone architecture and the *N*-aryl substituent of the thiazolium salts played a significant role in reaction efficiency (Table 1, entries 2–5). Employing 10 mol% carbene precursor **C**, such as the six-membered-ring thiazolium salt bearing *N*-2,6-diisopropylphenyl-substituent **C2**

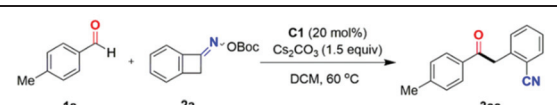
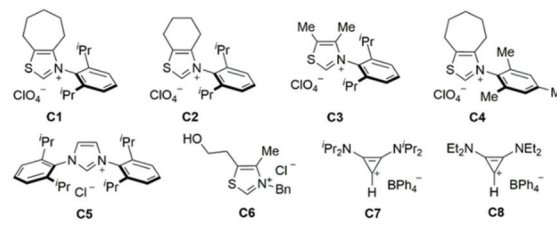
(entry 3), or the thiazolium salt with an acyclic backbone **C3** (entry 4), or the seven-membered-ring thiazolium salt bearing an *N*-mesityl-substituent **C4** (entry 5) resulted in reduced yields. The sterically demanding *N*-2,6-diisopropylphenyl group and a cycloheptane backbone were identified as the optimum structure (entry 2). Increasing the precatalyst **C1** loading to 20 mol% further boosted the product yield (entry 1). On the other hand, the commercially available imidazolium- and thiazolium-type NHC precatalysts **C5** and **C6** were quite ineffective in this transformation (entries 6 and 7), as were non-heterocyclic-based carbenes derived from bis(amino) cyclopropenium salts¹⁸ **C7** and **C8** (entries 8 and 9).

The solvent had a profound effect on the reaction, as other solvents including 1,2-dichloroethane (DCE), acetonitrile (MeCN), tetrahydrofuran (THF), and dimethyl sulfoxide (DMSO) were found to be unsuitable for this ring-opening acylation transformation (Table 1, entries 10–13). The choice of the base also proved to be the key. K₂CO₃ gave **3aa** in a comparable yield to Cs₂CO₃, whereas the use of other bases such as Na₂CO₃, DBU, or TMG instead of Cs₂CO₃ all led to a stark decrease in yield (entries 14–17). Control experiments revealed that the NHC catalyst and base were necessary for the success of this ring-opening acylation of oxime esters.

With the optimal reaction conditions in hand, the scope and limitations of this ring-opening acylation of oxime esters were investigated (Schemes 2 and 3). The initial focus was on assessing aldehyde diversity. As shown in Scheme 2, the C–C bond cleavage of benzocyclobutenone-derived oxime ester occurred with complete regioselectivity to form the more stable benzyl radical to engage in the reaction. When benzaldehyde **1b** was subjected to the standard conditions, the ketonitrile **3ba** was obtained in 86% yield. Benzaldehydes **1c–1h** bearing a gamut of pendant functionalities at the *para* position, such as ether (**3ca**), halides (**3da–3fa**), cyano group (**3ga**), and ester (**3ha**), were well accommodated, giving access to the corresponding coupling products **3ca–3ha** with yields ranging from 65% to 91%. Relatively lower reactivity was observed for 4-methoxybenzaldehyde **1c**, indicating that the introduction of a strong electron-donating group onto the aryl ring of the aldehyde might be detrimental for the aldehyde-derived Breslow radical intermediate to undergo radical–radical coupling with the benzyl radical. Although a substituent at the *para* and *meta* positions of the aryl aldehyde was tolerated (**3ea** and **3ja**), *o*-substituted benzaldehyde completely inhibited the reaction (data not shown). 2-Naphthaldehyde proved to be a viable coupling partner in this reaction manifold, affording the expected product **3ka** in 83% yield. Furthermore, aldehydes containing electron-rich and electron-deficient heteroaromatic rings such as thiophene and pyridine can also be used, as exemplified by **3la** and **3ma**. As a current limitation, aliphatic aldehydes are not competent as acyl donors in this reaction.

This may be attributed to the instability (short lifetime) of the aliphatic aldehyde-derived Breslow radical intermediate. Although cinnamaldehyde was also attempted, no products were observed. Finally, this organocatalytic approach was further applied to the late-stage modification of complex mole-

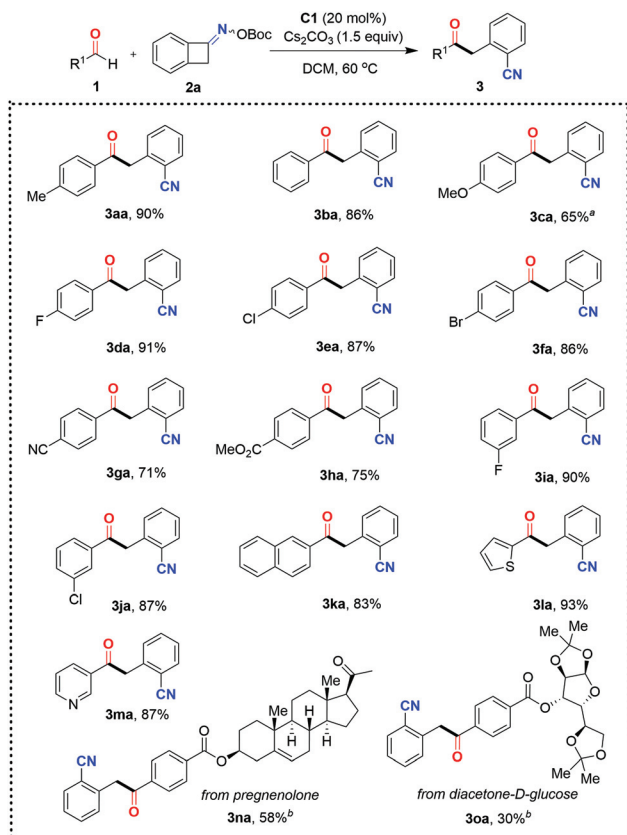
Table 1 Optimization of the reaction conditions^a

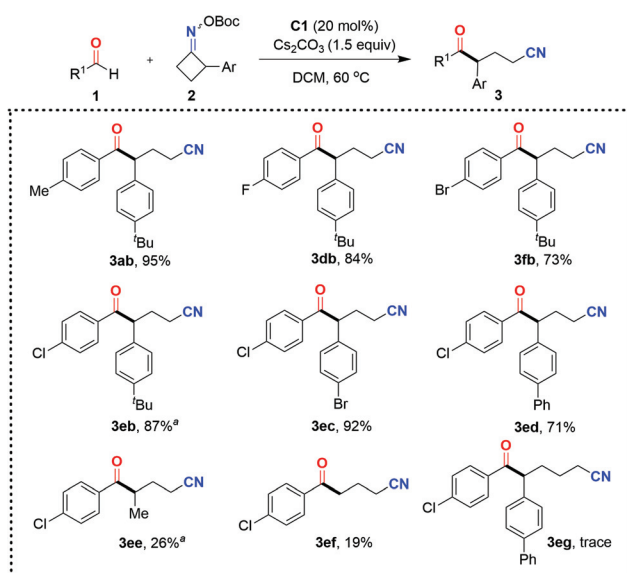
| Entry | Deviation from standard conditions | Yield ^b (3aa , %) |
|----------------|--|--------------------------------------|
| 1 | None | 95 |
| 2 | Using 10 mol% C1 | 66 |
| 3 ^c | C2 instead of C1 | 53 |
| 4 ^c | C3 instead of C1 | 40 |
| 5 ^c | C4 instead of C1 | 30 |
| 6 ^c | C5 instead of C1 | 1 |
| 7 ^c | C6 instead of C1 | 0 |
| 8 ^c | C7 instead of C1 | 0 |
| 9 ^c | C8 instead of C1 | 0 |
| 10 | DCE instead of DCM | 12 |
| 11 | MeCN instead of DCM | 1 |
| 12 | THF instead of DCM | 3 |
| 13 | DMSO instead of DCM | 0 |
| 14 | Na ₂ CO ₃ instead of Cs ₂ CO ₃ | 6 |
| 15 | K ₂ CO ₃ instead of Cs ₂ CO ₃ | 93 |
| 16 | DBU instead of Cs ₂ CO ₃ | 10 |
| 17 | TMG instead of Cs ₂ CO ₃ | 43 |
| 18 | No NHC catalyst | 0 |
| 19 | No base | 0 |

^a Reaction conditions: **1a** (0.1 mmol), **2a** (0.12 mmol), **C1** (20 mol%), and Cs₂CO₃ (0.15 mmol) in DCM (1.0 mL) at 60 °C for 12 h under Ar.

^b Yield determined by ¹H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard. ^c Using 10 mol% **C**. Boc = *tert*-butoxycarbonyl, DBU = 1,8-diazabicyclo[5.4.0]-7-undecene, and TMG = 1,1,1,3,3-tetramethylguanidine.



Scheme 2 Scope with respect to aldehydes. Standard reaction conditions: **1** (0.1 mmol), **2a** (0.12 mmol), **C1** (20 mol%), and Cs₂CO₃ (0.15 mmol) in DCM (1.0 mL) at 60 °C for 12 h under Ar; isolated yields based on **1** are given. ^a Using 40 mol% **C1**. ^b Using 30 mol% **C1**.



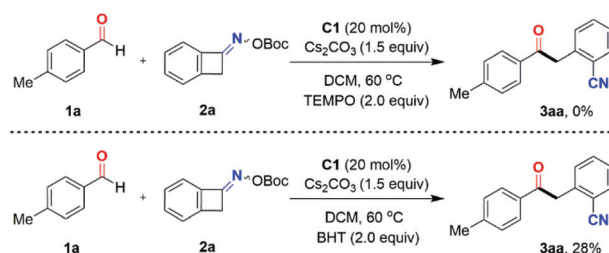
Scheme 3 Scope of the NHC-catalyzed ring-opening acylation of oxime esters. Reaction conditions: **1** (0.1 mmol), **2** (0.11 mmol), **C1** (20 mol%), and Cs₂CO₃ (0.15 mmol) in DCM (1.0 mL) at 60 °C for 12 h under Ar; isolated yields based on **1** are given. ^a 0.2 mmol scale.

cules. For example, complex aldehyde derivatives of pregnenolone and diacetone-D-glucose were apt to give serviceable yields of the coupling products **3na** and **3oa**. It is noteworthy that the thus obtained ketonitrile products **3** could be further converted to biologically active CWJ-a-5 analogues according to a reported procedure.¹⁹

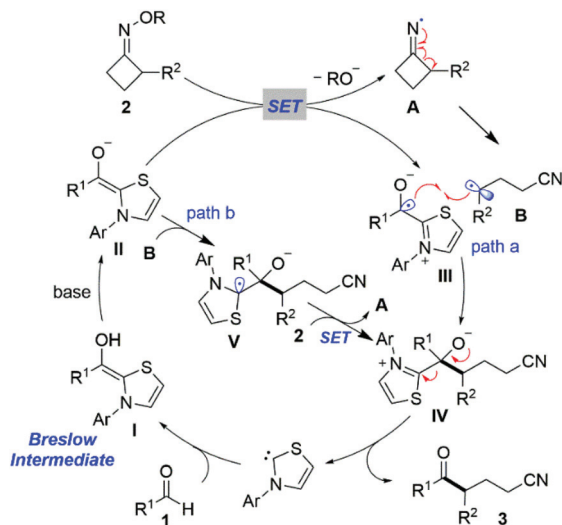
Our attention then turned to evaluating the scope of cycloketone oxime esters. Gratifyingly, the range of cycloketone oxime esters was not restricted to the benzocyclobutenone-derived oxime ester **2a**, and could also encompass α -aryl-substituted cyclobutanone-derived oxime esters (Scheme 3). The cyclobutanone oxime esters **2** with substituents such as tertiary butyl (**2b**), bromide (**2c**), and phenyl (**2d**) groups at the *para*-position of the aromatic ring reacted smoothly with 4-chlorobenzaldehyde **3e**, affording the corresponding products δ -keto nitriles (**3eb**, **3ec**, and **3ed**) with yields ranging from 71% to 92%. On the downside, the reaction performed poorly with the α -methyl-substituted cyclobutanone-derived oxime ester **2e** and non-substituted cyclobutanone-derived oxime ester **2f**, presumably due to the instability of the generated secondary or primary radical in comparison with the benzyl radical. The less-strained, five-membered cycloketone oxime ester **2g** was nonproductive under the present organocatalytic conditions. Only a trace amount of the target product **3eg** was detected by HRMS.

To shed light on the tentative reaction mechanism, a preliminary mechanistic investigation was performed (Scheme 4). In the presence of 2.0 equivalents of the radical scavenger 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO), the standard reaction of 4-methylbenzaldehyde **1a** and *O*-(*tert*-butoxycarbonyl) oxime **2a** was totally inhibited. Furthermore, 4-methylbenzaldehyde **1a** was reacted with *O*-(*tert*-butoxycarbonyl) oxime **2a** under standard conditions in the presence of 2.0 equivalents of the radical scavenger 2,6-di-*tert*-butyl-4-methylphenol (BHT), affording the two-component coupling product **3aa** in only 28% yield. This result indicated the radical nature of this transformation.

On the basis of the above experimental results and the literature,^{13a,16} a tentative mechanism for the NHC-catalyzed ring-opening acylation of oxime esters is illustrated in Scheme 5. First, NHC reacts with the aldehyde **1** to give the corresponding Breslow intermediate **I**. Next, the enolate form of the Breslow intermediate **II** would be generated by deprotonation in the presence of a base and induce the SET event



Scheme 4 Mechanistic investigations.



Scheme 5 Proposed mechanism for the NHC-catalyzed ring-opening acylation of oxime esters.

between the enolate **II** and cyclobutanone oxime ester **2**, affording a persistent ketyl radical **III** and an iminyl radical **A**, respectively. Subsequent regioselective ring-opening of **A** via C–C bond β -cleavage forms the benzyl radical **B**. Intermediates **III** and **B** would undergo radical–radical cross-coupling to furnish the intermediate **IV** (path a).²⁰ Alternatively, another addition of the benzyl radical **B** to the enolate form of the Breslow intermediate **II** might occur, giving a plausible NHC-bound radical intermediate **V**. SET from the intermediate **V** to oxime ester **2** would ensue to form the intermediate **IV** and a new iminyl radical **A**, respectively (path b). Currently, we cannot exclude either pathway. Ultimately, the species **IV** would undergo facile elimination to deliver the target product ketonitrile **3** and release the NHC, thereby closing this catalytic redox-neutral cycle.

Experimental

General procedure for ring-opening acylation of oxime esters

A flame-dried 10 mL resealable screw-cap Schlenk tube containing a magnetic stirring bar was charged with the aldehyde **1** (0.1 mmol, 1.0 equiv.), oxime ester **2** (0.12 mmol, 1.2 equiv.), NHC precursor **C1** (8.3 mg, 0.02 mmol, 0.2 equiv.), Cs₂CO₃ (48.9 mg, 0.15 mmol, 1.5 equiv.), and anhydrous DCM (1.0 mL) under an argon atmosphere. The reaction mixture was stirred in a preheated 60 °C oil bath for 12 h. After that, the mixture was concentrated under reduced pressure. The resulting crude product was purified by silica gel flash column chromatography to give the corresponding products **3aa–3ef**.

Conclusions

In summary, we have developed an emerging NHC-catalyzed radical cross-coupling of cycloketone oxime esters with readily

available aldehydes. By using an *N*-2,6-diisopropylphenyl-substituted cycloheptane-fused thiazolium salt as the NHC precatalyst, the cyanoalkyl or 2-cyanobenzyl from the cycloketone oxime esters and the acyl from the aldehydes were docked efficiently, giving access to ketonitriles in moderate to good yields. The aromatic nitriles can be used to construct a compound library of topoisomerase I inhibitor CWJ-a-5 analogues. This protocol features easy operation, with no need for external oxidants, reductants or transition-metal catalysts, and a good functional group tolerance. The compatibility of substrate scope covers benzocyclobutenone oxime esters, α -aryl-substituted cyclobutenone oxime esters, and aromatic aldehydes. Complicated aldehydes derived from the medical intermediate pregnenolone and natural product diacetone-D-glucose also proved to be viable coupling partners, affording the corresponding coupling products in synthetically useful yields. Mechanistic studies indicated that a radical pathway was involved. This work further enriches the types of radical reactions catalyzed by NHC.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

The support to this work by the National Natural Science Foundation of China (22078150), the Jiangsu National Synergetic Innovation Center for Advanced Materials (SICAM), the Priority Academic Program Development of Jiangsu Higher Education Institutions (PAPD), and the Top-Notch Academic Programs Project of Jiangsu Higher Education Institutions (TAPP) is gratefully acknowledged.

Notes and references

- For recent reviews, see: (a) M. N. Hopkinson, C. Richter, M. Schedler and F. Glorius, An overview of N-heterocyclic carbenes, *Nature*, 2014, **510**, 485–496; (b) D. M. Flanagan, F. Romanov-Michailidis, N. A. White and T. Rovis, Organocatalytic Reactions Enabled by N-Heterocyclic Carbenes, *Chem. Rev.*, 2015, **115**, 9307–9387.
- R. Breslow, On the Mechanism of Thiamine Action. IV.1 Evidence from Studies on Model Systems, *J. Am. Chem. Soc.*, 1958, **80**, 3719–3726.
- R. S. Menon, A. T. Biju and V. Nair, Recent advances in employing homoenolates generated by N-heterocyclic carbene (NHC) catalysis in carbon–carbon bond-forming reactions, *Chem. Soc. Rev.*, 2015, **44**, 5040–5052.
- C. Zhang, J. F. Hooper and D. W. Lupton, N-Heterocyclic Carbene Catalysis via the α,β -Unsaturated Acyl Azolium, *ACS Catal.*, 2017, **7**, 2583–2596.

- 5 R. Song and Y. R. Chi, N-Heterocyclic Carbene Catalyzed Radical Coupling of Aldehydes with Redox-Active Esters, *Angew. Chem., Int. Ed.*, 2019, **58**, 8628–8630.
- 6 For selected reviews, see: (a) T. Ishii, K. Nagao and H. Ohmiya, Recent advances in N-heterocyclic carbene-based radical catalysis, *Chem. Sci.*, 2020, **11**, 5630–5636; (b) J. Liu, X.-N. Xing, J.-H. Huang, L.-Q. Lu and W.-J. Xiao, Light opens a new window for N-heterocyclic carbene catalysis, *Chem. Sci.*, 2020, **11**, 10605–10613; (c) L. Dai and S. Ye, Recent advances in N-heterocyclic carbene-catalyzed radical reactions, *Chin. Chem. Lett.*, 2021, **32**, 660–667; (d) K.-Q. Chen, H. Sheng, Q. Liu, P.-L. Shao and X.-Y. Chen, N-heterocyclic carbene-catalyzed radical reactions, *Sci. China: Chem.*, 2021, **64**, 7–16; (e) Q.-Z. Li, R. Zeng, B. Han and J.-L. Li, Single-Electron Transfer Reactions Enabled by N-Heterocyclic Carbene Organocatalysis, *Chem. – Eur. J.*, 2021, **27**, 3238–3250; (f) H. Ohmiya, N-Heterocyclic Carbene-Based Catalysis Enabling Cross-Coupling Reactions, *ACS Catal.*, 2020, **10**, 6862–6869.
- 7 (a) N. Ikuo, I. Shinobu, S. Tomoyoshi, I. Hiroo and F. Shunichi, Redox Behavior of Active Aldehydes Derived from Thiamin Coenzyme Analogs, *Chem. Lett.*, 1997, **26**, 707–708; (b) I. Nakanishi and S. Itoh, Electron transfer properties of active aldehydes derived from thiamin coenzyme analogues, *Chem. Commun.*, 1997, 1927–1928, DOI: 10.1039/A704559J; (c) I. Nakanishi, S. Itoh, T. Suenobu and S. Fukuzumi, Direct Observation of Radical Intermediates While Investigating the Redox Behavior of Thiamin Coenzyme Models, *Angew. Chem., Int. Ed.*, 1998, **37**, 992–994; (d) I. Nakanishi, S. Itoh and S. Fukuzumi, Electron-Transfer Properties of Active Aldehydes of Thiamin Coenzyme Models, and Mechanism of Formation of the Reactive Intermediates, *Chem. – Eur. J.*, 1999, **5**, 2810–2818.
- 8 B. E. Maki, A. Chan, E. M. Phillips and K. A. Scheidt, Tandem Oxidation of Allylic and Benzylic Alcohols to Esters Catalyzed by N-Heterocyclic Carbenes, *Org. Lett.*, 2007, **9**, 371–374.
- 9 (a) J. Guin, S. De Sarkar, S. Grimme and A. Studer, Biomimetic Carbene-Catalyzed Oxidations of Aldehydes Using TEMPO, *Angew. Chem., Int. Ed.*, 2008, **47**, 8727–8730; (b) S. De Sarkar, S. Grimme and A. Studer, NHC Catalyzed Oxidations of Aldehydes to Esters: Chemoselective Acylation of Alcohols in Presence of Amines, *J. Am. Chem. Soc.*, 2010, **132**, 1190–1191.
- 10 (a) N. A. White and T. Rovis, Enantioselective N-Heterocyclic Carbene-Catalyzed β -Hydroxylation of Enals Using Nitroarenes: An Atom Transfer Reaction That Proceeds via Single Electron Transfer, *J. Am. Chem. Soc.*, 2014, **136**, 14674–14677; (b) N. A. White and T. Rovis, Oxidatively Initiated NHC-Catalyzed Enantioselective Synthesis of 3,4-Disubstituted Cyclopentanones from Enals, *J. Am. Chem. Soc.*, 2015, **137**, 10112–10115.
- 11 (a) Y. Zhang, Y. Du, Z. Huang, J. Xu, X. Wu, Y. Wang, M. Wang, S. Yang, R. D. Webster and Y. R. Chi, N-Heterocyclic Carbene-Catalyzed Radical Reactions for Highly Enantioselective β -Hydroxylation of Enals, *J. Am. Chem. Soc.*, 2015, **137**, 2416–2419; (b) B.-S. Li, Y. Wang, R. S. J. Proctor, Y. Zhang, R. D. Webster, S. Yang, B. Song and Y. R. Chi, Carbene-catalysed reductive coupling of nitrobenzyl bromides and activated ketones or imines via single-electron-transfer process, *Nat. Commun.*, 2016, **7**, 12933; (c) X. Wu, Y. Zhang, Y. Wang, J. Ke, M. Jeret, R. N. Reddi, S. Yang, B.-A. Song and Y. R. Chi, Polyhalides as Efficient and Mild Oxidants for Oxidative Carbene Organocatalysis by Radical Processes, *Angew. Chem., Int. Ed.*, 2017, **56**, 2942–2946.
- 12 (a) X.-Y. Chen, K.-Q. Chen, D.-Q. Sun and S. Ye, N-Heterocyclic carbene-catalyzed oxidative [3+2] annulation of dioxindoles and enals: cross coupling of homoenolate and enolate, *Chem. Sci.*, 2017, **8**, 1936–1941; (b) L. Dai, Z.-H. Xia, Y.-Y. Gao, Z.-H. Gao and S. Ye, Visible-Light-Driven N-Heterocyclic Carbene Catalyzed γ - and ϵ -Alkylation with Alkyl Radicals, *Angew. Chem., Int. Ed.*, 2019, **58**, 18124–18130; (c) L. Dai and S. Ye, Photo/N-Heterocyclic Carbene Co-catalyzed Ring Opening and γ -Alkylation of Cyclopropane Enal, *Org. Lett.*, 2020, **22**, 986–990; (d) L. Dai, Y.-Y. Xu, Z.-H. Xia and S. Ye, γ -Difluoroalkylation: Synthesis of γ -Difluoroalkyl- α,β -Unsaturated Esters via Photoredox NHC-Catalyzed Radical Reaction, *Org. Lett.*, 2020, **10**, 12960–12966.
- 13 (a) T. Ishii, Y. Kakeno, K. Nagao and H. Ohmiya, N-Heterocyclic Carbene-Catalyzed Decarboxylative Alkylation of Aldehydes, *J. Am. Chem. Soc.*, 2019, **141**, 3854–3858; (b) T. Ishii, K. Ota, K. Nagao and H. Ohmiya, N-Heterocyclic Carbene-Catalyzed Radical Relay Enabling Vicinal Alkylacylation of Alkenes, *J. Am. Chem. Soc.*, 2019, **141**, 14073–14077; (c) K. Ota, K. Nagao and H. Ohmiya, N-Heterocyclic Carbene-Catalyzed Radical Relay Enabling Synthesis of δ -Ketocarboxyls, *Org. Lett.*, 2020, **22**, 3922–3925; (d) Y. Kakeno, M. Kusakabe, K. Nagao and H. Ohmiya, Direct Synthesis of Dialkyl Ketones from Aliphatic Aldehydes through Radical N-Heterocyclic Carbene Catalysis, *ACS Catal.*, 2020, **10**, 8524–8529; (e) T. Ishii, K. Nagao and H. Ohmiya, Radical N-heterocyclic carbene catalysis for β -ketocarbonyl synthesis, *Tetrahedron*, 2021, 132212; (f) Y. Matsuki, N. Ohnishi, Y. Kakeno, S. Takemoto, T. Ishii, K. Nagao and H. Ohmiya, Aryl radical-mediated N-heterocyclic carbene catalysis, *Nat. Commun.*, 2021, **12**, 3848.
- 14 (a) W. Yang, W. Hu, X. Dong, X. Li and J. Sun, N-Heterocyclic Carbene Catalyzed γ -Dihalomethylenation of Enals by Single-Electron Transfer, *Angew. Chem., Int. Ed.*, 2016, **55**, 15783–15786; (b) J.-L. Li, Y.-Q. Liu, W.-L. Zou, R. Zeng, X. Zhang, Y. Liu, B. Han, Y. He, H.-J. Leng and Q.-Z. Li, Radical Acylfluoroalkylation of Olefins through N-Heterocyclic Carbene Organocatalysis, *Angew. Chem.*, 2020, **59**, 1863–1870; (c) H.-B. Yang, Z.-H. Wang, J.-M. Li and C. Wu, Modular synthesis of α -aryl β -perfluoroalkyl ketones via N-heterocyclic carbene catalysis, *Chem. Commun.*, 2020, **56**, 3801–3804; (d) B. Zhang, Q. Peng, D. Guo and J. Wang, NHC-Catalyzed Radical Trifluoromethylation Enabled by Togni Reagent, *Org. Lett.*,

- 2020, **22**, 443–447; (e) I. Kim, H. Im, H. Lee and S. Hong, N-Heterocyclic carbene-catalyzed deaminative cross-coupling of aldehydes with Katritzky pyridinium salts, *Chem. Sci.*, 2020, **11**, 3192–3197; (f) M.-S. Liu and W. Shu, Catalytic, Metal-Free Amide Synthesis from Aldehydes and Imines Enabled by a Dual-Catalyzed Umpolung Strategy under Redox-Neutral Conditions, *ACS Catal.*, 2020, **10**, 12960–12966; (g) L. Chen, S. Jin, J. Gao, T. Liu, Y. Shao, J. Feng, K. Wang, T. Lu and D. Du, N-Heterocyclic Carbene/Magnesium Cocatalyzed Radical Relay Assembly of Aliphatic Keto Nitriles, *Org. Lett.*, 2021, **23**, 394–399.
- 15 For selected reviews, see: (a) S. Z. Zard, Recent progress in the generation and use of nitrogen-centred radicals, *Chem. Soc. Rev.*, 2008, **37**, 1603–1618; (b) W. Yin and X. Wang, Recent advances in iminyl radical-mediated catalytic cyclizations and ring-opening reactions, *New J. Chem.*, 2019, **43**, 3254–3264; (c) T. Xiao, H. Huang, D. Anand and L. Zhou, Iminyl-Radical-Triggered C–C Bond Cleavage of Cycloketone Oxime Derivatives: Generation of Distal Cyano-Substituted Alkyl Radicals and Their Functionalization, *Synthesis*, 2020, **52**, 1585–1601; (d) X.-Y. Yu, J.-R. Chen and W.-J. Xiao, Visible Light-Driven Radical-Mediated C–C Bond Cleavage/Functionalization in Organic Synthesis, *Chem. Rev.*, 2021, **121**, 506–561; (e) W. Xiao and J. Wu, Recent advances for the photoinduced CC bond cleavage of cycloketone oximes, *Chin. Chem. Lett.*, 2020, **31**, 3083–3094.
- 16 Y. Gao, Y. Quan, Z. Li, L. Gao, Z. Zhang, X. Zou, R. Yan, Y. Qu and K. Guo, Organocatalytic Three-Component 1,2-Cyanoalkylacylation of Alkenes via Radical Relay, *Org. Lett.*, 2021, **23**, 183–189.
- 17 In our previous work (*Org. Lett.*, 2021, **23**, 183–189), we recorded two-component coupling reactions between a cycloalkane oxime and an aldehyde, and during preparation of this manuscript, an independent work employing cyclopentanone oxime as the substrate was disclosed. H.-B. Yang and D.-H. Wan, C–C Bond Acylation of Oxime Ethers via NHC Catalysis, *Org. Lett.*, 2021, **23**, 1049–1053.
- 18 M. M. D. Wilde and M. Gravel, Bis(amino)cyclopropenylenes as Organocatalysts for Acyl Anion and Extended Umpolung Reactions, *Angew. Chem., Int. Ed.*, 2013, **52**, 12651–12654.
- 19 K. Yashiro, K. Sakata, I. Hachiya and M. Shimizu, Titanium tetraiodide induced cyclization of cyanoketones into 3-Aryl-1-Iodoisoquinolines, *Heterocycles*, 2016, **92**, 2032–2046.
- 20 D. Leifert and A. Studer, The Persistent Radical Effect in Organic Synthesis, *Angew. Chem.*, 2020, **59**, 74–108.